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APPARATUS AND METHOD FOR CONDUCTING ASSAYS

EXHIBIT "A"

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
JOHN FRANCIS GORDON
Serial No.: 09/284,421
Filed: June 11, 1999
Title: APPARATUS AND METHOD FOR CONDUCTING ASSAYS

Examiner: Bex, P. Kathryn
Group Art Unit: 1743
Attorney Docket No. 18950-37

CERTIFICATE UNDER 37 CFR 1.8(a)

I hereby certify that on July 29, 2002 this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Commissioner of Patents, Washington, D.C. 20231.

By: Florence Thys-Doucet
Name: Florence Thys-Doucet

AMENDMENT

Honorable Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Action of January 29, 2002, please amend the above-identified application as follows:

In the Claims:

Please amend the pending elected claims as follows, a marked up copy showing the claim amendments is appended hereto:

89. (Amended) A multi-reaction site assay plate structure comprising an upper surface and a lower closely spaced opposed surface, said upper and lower surfaces defining a space therebetween, the lower surface having a plurality of separate reaction sites, the reaction sites being treated to increase the hydrophilicity thereof, and the lower surface being treated to increase the hydrophobicity of the surface other than at said reaction sites, at least one opening providing access to said space from an external location, the spacing between said upper and lower surfaces being provided to facilitate the flow of fluid in said space by capillary action of a fluid introduced into said space through said opening to substantially fill the space and cover all

of the sites, the sites being such that when excess fluid is subsequently withdrawn through the one or another opening some of said liquid is left at said sites.

99. (Twice Amended) The assay plate structure of claim 98 wherein the plate structure is transparent for optical inspection of said wells and encoded information from outside the disc.

105. (Amended) An optically transparent structure for conducting assays comprising one or more chambers, each having an upper surface and a lower spaced opposed surface, said upper and lower surfaces defining a space therebetween, the lower surface having a plurality of surface locations bearing a hydrophillic coating, the spacing between said upper and lower surfaces being provided to facilitate fluid flow by capillary action of a fluid introduced into said space to cover all of the locations bearing a hydrophillic coating.

108. (Amended) The structure of claim 105 wherein said surfaces are provided by respective upper and lower plates of a disc.

110. (Amended) The structure of claim 108 including digitally encoded address information provided for optical inspection thereof from exteriorly of said structure.

123. (Amended) A multi-reaction site assay plate structure comprising an upper surface and a lower opposed surface, said upper and lower surfaces defining a space therebetween, the lower surface having a plurality of separate reaction sites, the reaction sites being treated to increase the hydrophilicity thereof, and the lower surface being treated to increase the hydrophobicity of the surface other than at said reaction sites, the spacing between said upper and lower surfaces being provided to facilitate the flow of fluid in said space by capillary action of a fluid introduced into said space through said opening to cover all of the sites.

131. (Amended) The assay plate structure of claim 126 wherein the plate structure includes digitally encoded address information.

In the Specification:

Please amend the specification as follows, a marked up copy showing the claim amendments being amended hereto:

Page 13, please amend the paragraph beginning at line 26 which continues through line 10 on page 14 as follows. A marked up copy of the claimed amendment being appended hereto.

Each disk sector 62 is arranged to receive a sector plate insert 64 which is a transparent polycarbonate plate with a detachable handle 66 on the outer side to facilitate entry and removal of the plate insert 64 in the sector 62. The plate insert 64 and spacer wall 60 have respective recesses/projections (not shown in the interest of clarity) which allow the plate insert 64 to be inserted only in the correct orientation. The plate insert 64 has a groove 68, as shown in Fig. 4b for example, which allows the inset to be snap-fitted over a projection 70 upstanding from plate 58 into the sector. The thickness of the sector plate insert 64 is marginally less than the spacing provided between the upper and lower plates 56, 58 so that the plate insert 64 can be pressed/fitted into one of the disk sector 62 to define a liquid receiving chamber or space 73 between the upper surface 64a of the plate insert 64 and the lower surface 56a of the upper disk plate 56. Openings 72 are provided through the upper disk plate 56into each disk sector 64 whilst the space 70 between the radially outermost peripheral edge 74 of the insert plate 64 and the upper plate 56 provides a further vent or filing opening into the disk sector 62.

Page 18, please amend the paragraph beginning at line 5 which continues through line 24 on page 19 as follows. A marked up copy of the claimed amendment being appended hereto.

It will be appreciated that modification may be made to the above described embodiments without departing from the scope of the present invention. For example, the opening through which a liquid analyte is introduced may be provided through the lower plate of the multi-well container. More than one opening can be used for faster flooding. This opening may be arranged to receive the tip of a syringe needle. The vent opening may also be provided in any one of the walls of the container although it is preferably provided in a peripheral wall.

The opening 22 may be provided by a single opening 22 or by a series of openings or vents as shown in Fig. 4d for example. A laser may be used with CD optics instead of the microscope and video camera for the embodiment of Fig. 4. The top plate in the embodiment of Figs. 3 and 4 may be snap-fitted to the lower plate and may be snap-fitted onto a CD base plate which would receive sections and provide the advantage of positioned information. As shown in Fig. 4c the upper planar surface 56 can have sector covers connected to a lower surface or central boss by a hinge, for example integrated living hinge 90 at the inner radius to allow each disk sector 62 to be pivotally raised and lowered and allow sector plates 64 to be inserted into each sector. The well size and spacing may be varied as required, for example the wells could be 3mm in diameter; 1.5mm apart and spaced 5.5mm between centre. The exact size and spacing is a matter of choice consistent with the requirement that fluid is retained in the wells after withdrawal as described above. However, the wells could also be filled during flooding of the space depending on the well size, type of plastic and fluid properties. However, liquid will still be retained in the wells upon withdrawal of the liquid. Also, the structure and inserts made may be of any suitable optically transmissive plastic, such as polystyrene or perspex™. The handle 66 may be integrated with or detachable from plate 64. As shown in Fig 4a the radially extending ribs may have radial shoulders 92 to define a recess 94 for receiving the plate 64 also defining the spacing height between the surface 64a of the plate 64 and the underside 56a for receiving the liquid. Suitable materials may be used to coat the interior of the sectors to aid fluid movement as described with reference to silicone above. This may be applied to the underside of the top surface and to the top surface of the plats as for the other embodiments. Suitable materials maybe used to increase the hydrophobicity of liquid across the sector and hydrophilicity to the movement of liquid into the desired location, e.g. wells. The wells may be coated with a suitable optical reflective material to enhance the reflection of light and observation of reactions occurring within the wells and, similarly, lenses 90 may be located in the top or bottom light transmissive plates 12 and 14 as seen in Fig. 8, to improve optical assessment of the reaction. These lenses may be moulded into the upper or lower plates of the exemplary embodiments during the manufacture as is well known in plastic moulding processes. Separate optical elements may be used instead, if appropriate.

In the Drawings:

Please amend Fig. 4b to correct reference 64a and amend Fig. 4d to correct reference 64 and 64a, and add reference 66, all as indicated in red line on the appended sheet of drawings showing Figs. 4b and 4d.

Please approve the addition of Fig. 8 presented herewith which follows the format of Fig. 2d with the location of lenses 90 described in the specification indicated. Approval of the drawing amendments and addition are requested.

REMARKS

The office action of January 29, 2002, the references cited and the examiner's comments thereon have been carefully considered. Applicant, through undersigned counsel, wishes to affirm the election of Claims 89-99 and 105-135, Group IV as previously made in a telephone interview of January 16, 2002.

Considering the drawing corrections required by paragraphs 8 and 9 of the office action, the reference character 64 is intended for use with the plate insert only, the specification having been amended at page 13 to provide such conformity. Proposed drawing corrections for Figs. 4a and 4d are presented to amplify and clarify the reference numerals 64, 64a and 66 as referred to in the specification. A new Fig. 8 is presented for the examiner's approval herein which shows the location of the one or more lenses described in the application specification at page 13, lines 15 through 24. The specification has been amended to refer to the lenses as being indicated by the reference numeral 90 as seen in association with the plates 12 and 14 in Fig. 8. It is submitted that no new matter is being presented in simply showing the location of the lenses in the plates as indicated by the specification. Approval of the drawing corrections to Figs. 4a and 4d, and the addition of Fig. 8 are requested.

Claim 99 has been amended to delete "an" as suggested in paragraph 10 of the office action.

Claim 108 has been amended to delete "optical" in favor of disk as suggested in paragraph 12 of the office action. Claims 110 and 131 have been amended to change their dependency in order to clarify the environment within which the encoded information is being provided.

It is respectfully submitted that the specification supports a claim such as 117 wherein the claim limitation is recited in the environment of generic claim 105. Claim 105 is generic to all the embodiments and it is not necessary to limit a dependent claim to any specific embodiment. As pointed out by the examiner, the specification describes a third embodiment, see Fig. 4, which shows the disk assay plate 54 having a plurality of disk sectors arranged to receive a sector insert. It is submitted that these features need not be inserted into the claim, the combined claims 105 and 117 reciting a patentable structure supported by the disclosure.

Claims 121-122 are supported by the specification disclosure of the provision of one or more lenses molded into the structure. The specification recitation of page 19 is illustrated in proposed Fig. 8. It is submitted that these claims are supported by the specification.

Considering the issues of paragraph 14 of the office action, claims 89, 105 and 123 have been amended to remove "sufficiently small", such language being replaced by the phrase "provided." It is submitted that these claims are now definite within the meaning of 35 USC § 112.

The phrase "such that" and the accompanying language has been deleted from claim 123 in order to render the claim definite in view of the examiner's comments of paragraph 14. It is submitted that these claims are now in compliance with the requirements of 35 USC § 112.

Claims 89-91, 96, 105-107, 109 and 123-124 have been rejected as being anticipated by Fox within the provisions of 35 USC § 102. It is respectfully submitted that the office action mischaracterizes the teachings of the Fox reference. In the disclosure of the Fox US Patent No. 5, 041,266, particularly Fig. 6, the tray disclosed does not include an inlet 44 which allows fluids

to be introduced and withdrawn from the chamber between a mat 40 and a tray 22 via "a fluid introducing device 50."

Device 50 is actually an electrode and so called upper surface 40 is actually an electron shield mat. The patent discloses the provision of the electron shield mat 40 over the tray 22 so as to cover side walls 46 of a tray well 25 so electrons impact only the well bottom surface 32 thus rendering only surface 32 as hydrophillic. (See column 5, lines 46-56). In the example 1 process, (see column 8, lines 25 *et seq.*) a micro drop was added to the shielded treatment tray by directing the micro drop to a side wall 46 of a tray well 25 wherein "the droplet immediately rolled down the side of the well and spread evenly across the bottom of the well." In non-treated wells, the droplet clung to the side wall 46. It is thus apparent that the shield 40 is used only in processing the tray and that no fluid is introduced through or between mat 40 and the underlying tray 42.

The second primary reference of Croteau Patent No. 5,700,655 shows in incubation plate 10 having wells 12. A cover 14 as seen in Fig. 1A can be placed over the plate 10. In column 5, lines 20 *et seq.*, the specification suggests that liquid added to plate 10 can be "swirled within incubation plate 10 to distribute the inoculated liquid reagent to each of wells 12." The plate is then held at an angle of approximately 90° to allow excess liquid to be removed from the plate. The disclosure states that liquid can be removed through the pour spout 24 when the lid slit is aligned. There is no suggestion of adding liquids when the lit is in place. Moreover, in the "use" section, (column 5, line 25 *et seq.*: the lid is placed on the plate after excess liquid is removed. It is thus apparent that liquid is moved by the swirling action, not by any capillary action provided between closely spaced plates.

It is thus apparent that the primary reference Fox fails to anticipate the claims presented in this application. Furthermore, the secondary reference does not suggest any modification of the Fox reference which could cause it to be anticipatory of applicant's currently presented claims which emphasize the spacing between the upper and lower surfaces being provided to facilitate fluid flow by capillary action of a fluid introduced into the space as recited in

applicant's claims. This construction and mode of operation is not found in the references noted. It is respectfully submitted that the 35 USC § 102 rejection should be withdrawn.

Considering now the rejection of paragraph 20, claims 90-92 are dependant on claim 89 which is not rejected under 35 USC § 103. Claims 90-92 are not directed to modular sectors as discussed in paragraph 20 of the office action but rather are directed to features of claim 89 in the spacing of the upper and lower surfaces and the provision of the opening for introducing fluid into such space. The Croteau et al. reference taken in view of Zanzucchi teaches nothing about the limitations of claims 90-92 in the environment of their parent claim 89.

Claims 94-95 are dependant upon claims 89 and 93 which are not rejected under the 35 USC § 103 rejection. It is submitted that the limitation of claim 94 in having a second opening provided at the peripheral edge of the disc recited is not suggested by the Croteau and Zanzucchi references discussed in paragraph 20. Claim 95 further defines the structure of claims 89, 93 and 94 wherein the space between the upper and lower plates is subdivided by one or more dividing walls to provide a plurality of spaces, each space being provided with a fluid introduction opening and a vent opening to enable each space to be independently filled. It is respectfully submitted that this construction recited in claim 95 is patentably distinct within the environment of its parent claims 89 93 and 94.

The primary reference of Croteau really suggests that liquid added to plate 10 can be "swirled within incubation plate 10 to distribute the inoculated liquid reagent to each of the wells 12". There is no suggestion of adding liquids when the lid is in place. The secondary, Zanzucchi reference shows the disc 14 having module 48 locations formed in the disc, which are not inserts. Fluid flow is radially inwardly from inlet 50 or loading channel 34 toward the locations 40, 42, 44 by means of external pumping action or miniature pumps provided on the disc. Liquid in a capillary tube 32 is loaded by placing the tube 32 into the loading channel 34. There is no handle for manipulating an insert into a disc, the reference merely showing a capillary tube 32 being inserted into a loading channel 34. It is submitted that this secondary

reference does not make a suggestion as to how the Croteau tray might be modified in any manner to meet the claims put in issue in paragraph 20 of the office action.

Claim 111 discussed in paragraph 20 of the office action, describes a liquid injecting device, said one opening a forming a substantially air-tight seal around the end of the liquid injecting device. It is submitted that this structure is not shown in the references and not in the environment of claim 111 which is dependent upon claims 105 and 106. Similarly, claims 113-115 are directed to a second opening in addition to the first opening which is provided at a peripheral edge of the disc to vent the space (113) and where the space is subdivided (114) with the dividing walls being radially extending (115) within the environment of their parent claims 112 and 105. It is submitted that the primary and secondary references do not suggest the combination thus claimed.

Claim 117 is directed to the structure of claim 105 arranged to receive one or more inserts. The primary and secondary references do not suggest inserts, there being only the showing of a capillary sample tube being added to a loading channel. It is submitted that the construction of claim 117 in the environment of its parent claim 105 is not suggested by the references. Similarly, claim 125, dependent upon its parent claims 124 and 123, is directed to the feature of the opening providing access to the space having a substantially air-tight seal around an end of a liquid injecting device to be received in the opening. This construction and mode of operation is not suggested in the references. Claim 127 adds the feature of a second opening provided at the peripheral edge of the disc as recited in parent claims 123 and 126. It is submitted that this construction in the environment of its parent claims is not suggested by the references. Claim 128 adds the further limitation to claim 127 of the space between the upper and lower surfaces being divided by one or more dividing walls into a plurality of spaces as recited in the claim. It is submitted that this construction and mode of operation is not suggested by the references within the environment of the parent claims 127, 126 and 123.

The rejection of paragraph 21 repeats the principle reference of Croteau presumably modified in view of Merkh. Considering the objections of paragraph 21 of the office action it is

noted that claims 90-92, dependant upon claim 89, are not related to a disc structure which is divided into removable sectors. It is submitted that claims 90-92 are patentably distinct over the references in the environment of their parent claim 89. Similarly, claims 98 and 99 are dependent upon claim 89 which is not rejected under the 35 USC § 103 rejection. Claim 98 adds the limitation of digitally encoded information while claim 99 is directed to the structure being provided for use with a device having an optical reading apparatus type format. It is submitted that these claim limitations in the environment of their parent claim 89 are patentably distinct over the references.

Claims 110-120 are dependent from claim 105 which has not been rejected under the 35 USC § 103 rejection. Claims 125-129 are dependant on at least claim 123 which has not been rejected under the 35 USC § 103 rejection. The same is true for claim 131 which is dependant upon claim 123. It is submitted that the limitations of the claims referred to in paragraph 21 are patentably distinct in the environment of their parent claims which have not been rejected under the 35 USC § 103 rejection. The primary and secondary references relied upon by the examiner in rejecting these claims do not address the fundamental relationship of the claimed components in the parent claims from which these claims depend.

Considering now the rejection of paragraph 22, the primary reference Croteau fails to teach the basis structure of claims 97 and 130 which are respectively dependant upon their parent claims 96, 93 and 89 as to claim 97 and claims 129, 126 and 123 as to claim 130. The reflective surface of claims 97 and 130 is provided in association with a transparent upper or lower plate of the structure, a combination and construction not suggested in Takase.

Considering the comments of paragraph 23 of the office action, the Ford reference merely discloses a diagnostic microscope slide having thin transparent lenses in the cover and base above and below the sample well. This reference merely discloses applicant's specification statement that the provision of lenses as described is per se known in the art. However, applicant's lenses are being provided within a structure and environment of claim 121-122 to cooperate with the structure of claim 105. It is submitted that the primary and secondary

references do not suggest that basic arrangement of structure of claim 105 nor the specific overall arrangement of the structure of claims 105 and as then specified in the dependant claims 121 and 122.

In view of the foregoing, reconsideration and allowance of all elected claims presently submitted is hereby requested.

Applicant applies for a three month extension of time to respond to the office action of January 29, 2002. A check in the amount of $920 accompanies this request. The Commissioner is hereby authorized to charge any additional filing fees under 37 C.F.R. § 1.16, or application processing fees under 37 C.F.R. § 1.17, which may be required now or during the pendency of this application, or credit any overpayment to Account No. 16-2230.

Respectfully submitted,

Dated: July 29, 2002

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Marked up Copy of the Specification to Show Changes

Page 13, please amend the paragraph beginning at line 26 which continues through line 10 on page 14 as follows. A marked up copy of the claimed amendment being appended hereto.

Each disk sector 62 is arranged to receive a sector plate insert 64 which is a transparent polycarbonate plate with a detachable handle 66 on the outer side to facilitate entry and removal of the plate insert 64 in the sector 62. The plate insert 64 and spacer wall 60 have respective recesses/projections (not shown in the interest of clarity) which allow the [assay] plate insert 64 to be inserted only in the correct orientation. The plate insert 64 has a groove 68, as shown in Fig. 4b for example, which allows the inset to be snap-fitted over a projection 70 upstanding from plate 58 into the sector. The thickness of the sector [insert] plate insert 64 is marginally less than the spacing provided between the upper and lower plates 56, 58 so that the plate insert 64 can be pressed/fitted into one of the disk sector 62 to define a liquid receiving chamber or space 73 between the upper surface 64a of the [insert] plate insert 64 and the lower surface 56a of the upper disk plate 56. Openings 72 are provided through the upper disk plate 56into each disk sector 64 whilst the space 70 between the radially outermost peripheral edge 74 of the insert plate 64 and the upper plate 56 provides a further vent or filing opening into the disk sector [64] 62.

Page 18, please amend the paragraph beginning at line 5 which continues through line 24 on page 19 as follows. A marked up copy of the claimed amendment being appended hereto.

It will be appreciated that modification may be made to the above described embodiments without departing from the scope of the present invention. For example, the opening through which a liquid analyte is introduced may be provided through the lower plate of the multi-well container. More than one opening can be used for faster flooding. This opening may be arranged to receive the tip of a syringe needle. The vent opening may also be provided in any one of the walls of the container although it is preferably provided in a peripheral wall. The opening 22 may be provided by a single opening 22 or by a series of openings or vents as shown in Fig. 4d for example. A laser may be used with CD optics instead of the microscope and video camera for the embodiment of Fig. 4. The top plate in the embodiment of Figs. 3 and 4 may be

snap-fitted to the lower plate and may be snap-fitted onto a CD base plate which would receive sections and provide the advantage of positioned information. As shown in Fig. 4c the upper planar surface 56 can have sector covers connected to a lower surface or central boss by a hinge, for example integrated living hinge 90 at the inner radius to allow each disk sector 62 to be pivotally raised and lowered and allow sector plates 64 to be inserted into each sector. The well size and spacing may be varied as required, for example the wells could be 3mm in diameter; 1.5mm apart and spaced 5.5mm between centre. The exact size and spacing is a matter of choice consistent with the requirement that fluid is retained in the wells after withdrawal as described above. However, the wells could also be filled during flooding of the space depending on the well size, type of plastic and fluid properties. However, liquid will still be retained in the wells upon withdrawal of the liquid. Also, the structure and inserts made may be of any suitable optically transmissive plastic, such as polystyrene or perspex™. The handle 66 may be integrated with or detachable from plate 64. As shown in Fig 4a the radially extending ribs may have radial shoulders 92 to define a recess 94 for receiving the plate 64 also defining the spacing height between the surface 64a of the plate 64 and the underside 56a for receiving the liquid. Suitable materials may be used to coat the interior of the sectors to aid fluid movement as described with reference to silicone above. This may be applied to the underside of the top surface and to the top surface of the plats as for the other embodiments. Suitable materials maybe used to increase the hydrophobicity of liquid across the sector and hydrophilicity to the movement of liquid into the desired location, e.g. wells. The wells may be coated with a suitable optical reflective material to enhance the reflection of light and observation of reactions occurring within the wells and, similarly, lenses 90 may be located in the top or bottom light transmissive plates 12 and 14 as seen in Fig. 8, to improve optical assessment of the reaction. These lenses may be moulded into the upper or lower plates of the exemplary embodiments during the manufacture as is well known in plastic moulding processes. Separate optical elements may be used instead, if appropriate.

Marked Up Copy of the Claims to Show Changes

89. (Amended) A multi-reaction site assay plate structure comprising an upper surface and a lower closely spaced opposed surface, said upper and lower surfaces defining a space therebetween, the lower surface having a plurality of separate reaction sites, the reaction sites being treated to increase the hydrophilicity thereof, and the lower surface being treated to increase the hydrophobicity of the surface other than at said reaction sites, at least one opening providing access to said space from an external location, the spacing between said upper and lower surfaces being [sufficiently small] provided to facilitate the flow of fluid in said space by capillary action of a fluid introduced into said space through said opening to substantially fill the space and cover all of the sites, the sites being such that when excess fluid is subsequently withdrawn through the one or another opening some of said liquid is left at said sites.

99. (Twice Amended) The assay plate structure of claim 98 wherein the plate structure is transparent for [an] optical inspection of said wells and encoded information from outside the disc.

105. (Amended) An optically transparent structure for conducting assays comprising one or more chambers, each having an upper surface and a lower spaced opposed surface, said upper and lower surfaces defining a space therebetween, the lower surface having a plurality of surface locations bearing a hydrophillic coating, the spacing between said upper and lower surfaces being [sufficiently small] provided to facilitate fluid flow by capillary action of a fluid introduced into said space to cover all of the locations bearing a hydrophillic coating.

108. (Amended) The structure of claim 105 wherein said surfaces are provided by respective upper and lower plates of [an optical] a disc.

110. (Amended) The structure of claim [105] 108 including digitally encoded address information provided for optical inspection thereof from exteriorly of said structure.

123. (Amended) A multi-reaction site assay plate structure comprising an upper surface and a lower opposed surface, said upper and lower surfaces defining a space therebetween, the lower surface having a plurality of separate reaction sites, the reaction sites being treated to increase the hydrophilicity thereof, and the lower surface being treated to increase the hydrophobicity of the surface other than at said reaction sites, the spacing between said upper and lower surfaces being [sufficiently small] provided to facilitate the flow of fluid in said space by capillary action of a fluid introduced into said space through said opening to cover all of the sites[, the sites being such that when excess fluid is subsequently withdrawn through the one or another opening some of said liquid is left at said sites].

131. (Amended) The assay plate structure of claim [123] 126 wherein the plate structure includes digitally encoded address information.